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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,860	09/24/2004	Mitsuru Sakai	Q83342	8710

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,860	SAKAI ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on 05/27/08 is acknowledged. Claims 1-8 are pending in the application.

Response to Amendment

2. Claims objection and rejected under 35 U.S.C. 112, second paragraph, are withdrawn in light of the amended. Rejection over the prior art is maintained.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. **Claims 1-6** are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchholz et al. (Anal. Biochem., 2001) (Buchholtz) in view of Hosokawa et al. (Anal. Biochem., 1986) (Hosokawa).

Buchholz teaches "quantification of intracellular metabolites in *Escherichia coli* K12 using liquid chromatographic-electrospray ionization tandem mass spectrometric techniques" (Title), including assaying concentrations of Coenzyme A molecules (acetyl-CoA). The method comprises adding cGMP as an internal standard to the cell pellets, adding perchloric acid, storing cells at -80°C, centrifuging and neutralizing the supernatant and performing HPLC-ESI-MS-MS analysis (Abstract and page 131, right column).

Buchholz does not specifically disclose a step of solid phase extraction of the sample and using a structural analog of the coenzyme A as an internal standard.

Hosokawa teaches "determination of short-chain acyl-coenzyme A esters by high-performance liquid chromatography" with esters obtained from tissue. The method comprises extraction from freeze-clamped rat livers with perchloric acid, applying the extract to Sep-Pak C18 cartridge (solid phase extraction with octadecylsilyl group) and eluting the extract with ethanol/water containing ammonium acetate. The eluate is separated by HPLC using reverse-phase columns with linear gradient of acetonitrile. Isobutyryl-CoA is used as an internal standard (Claim 6) (Abstract).

It would have been obvious for a person of ordinary skill in the art to apply the step of solid phase extraction of the coenzymes with experimental conditions taught by Hosokawa to

Buchholz' method, because it allows a better separation of such analogous compounds as malonyl-CoA, saccinyl-CoA, acetyl-CoA, acetoacetyl-CoA, and propionyl-CoA, as indicated by Hosokawa (see Abstract).

It would have been obvious for a person of ordinary skill in the art to add the internal standard after the step of solid phase extraction in order to not loose the internal standard during extraction step, since it is a quantitative reference for the analyzed compound; also, internal standards are conventionally used in quantitative MS analysis.

5. **Claims 7 and 8** are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchholz in view of Hosokawa, as applied to claims 1-6 above, and further in view of e.g. Reszko et al. (Anal. Biochem., 2001, IDS) (Reszko).

Buchholz in view of Hosokawa do not specifically teach using ^{13}C or ^{2}H-labeled internal standards.

Using stable-isotope internal standards having structures analogous to that of analytes is a conventional technique for quantitative MS. Reszko teaches [U-$^{13}C_3$]malonyl-CoA or dimethylmalonyl-CoA internal standards for assaying short-chain acyl-CoA fraction using GC-MS.

It would have been obvious for a person of ordinary skill in the art to use ^{13}C labeled internals disclosed by Reszko in Buchholz-Hosokawa's method, because utilizing stable-isotope internal standards with structures analogous to those of analytes is a conventional technique in quantitative MS analysis.

It would have been obvious for a person of ordinary skill in the art to use deuterium-enriched internal standards instead of ^{13}C-enriched internal standard, because they are much easier to obtain and they are cheaper than ^{13}C-enriched standards. Also, deuterated internal standards for quantifying analytes are conventionally used in mass spectrometry.

Response to Arguments

6. Applicant's arguments filed 05/27/08 have been fully considered but they are not persuasive. The Applicants argue that there would not have been a motivation for a person of ordinary skill in the art to combine Hosokawa, who teaches a solid-phase extraction step for partially purifying CoA compounds, with Buchholz' method of "quantification of intracellular

metabolites in *Escherichia coli* K12 using liquid chromatographic-electrospray ionization tandem mass spectrometric techniques" (Title), including assaying concentrations of Coenzyme A molecules (acetyl-CoA), because this "would destroy the operability of the method of Buchholz for the intended purpose". The examiner respectfully disagrees. While Buchholz applies his method for quantification of multiple intracellular metabolites, specific quantification of some of them, i.e. Coenzyme A molecules, would have been an obvious modification and a simpler version of Buchholz' method, with solid-phase extraction of these particular metabolite components taught by Hosokawa. The examiner considers simplifying a method with its corresponding modification not being equivalent to destroying the method. While Buchholz teaches quantifying all intracellular metabolites, including Coenzyme A molecules, the quantification of specifically Coenzyme A molecules with their preliminary solid phase extraction is an obvious modification of Buchholz' more complex method. Again, from the examiner's point of view, the simplification of the method, when only a part of metabolites is quantified with their preliminary solid-phase extraction is not destroying of the method, but rather its obvious modification. Also, the examiner cannot agree with the Applicants' position that there is no reasonable expectation of success for the combined Buchholz-Hosokawa method. It is not clear, as to what is the basis for such conclusion. If Buchholz was capable of quantifying all (or most) of intracellular metabolites, including specific CoA molecules, why would quantification of only those CoA molecules which were preliminary extracted using solid-phase extraction technique would not have a reasonable expectation of success?

Regarding using internal standard in quantitative MS analysis, using the internal standards is conventional for quantitative MS. Hosokawa teaches using the internal standard for HPLC analysis, which can be used for MS analysis, because it meets all well known requirements for the internal standard used for MS analysis; specifically it possesses the structuer closely related to that of the analyte.

Regarding the Applicants' arguments related to rejections of claims 7 and 8, the examiner agrees that no "fancy" motivation of using internal standards for quantitative mass spectrometry were necessary, because using stable isotope internal standards is conventional in the field of quantitative mass spectrometry. Reszko specifically discloses such ^{13}C enriched internal

standards, with deuterium standards being an obvious modification because of their lower price and better availability than ^{13}C labeled standards.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/

Primary Examiner, Art Unit 1797

07/24/2008